E-cigarette, or Vaping Product-Associated Lung Injury (EVALI):

Seeking the Toxicant(s)

Society of Toxicology Meeting
Anaheim, CA
March 15, 2020

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Environmental Health Investigations Branch
California Department of Public Health
Richmond, CA
U.S. National EVALI Statistics (Feb, 2020)

Outbreak of Lung Injury Associated with the Use of E-Cigarette, or Vaping, Products

Centers for Disease Control and Prevention:

- 2758 EVALI cases nationwide (all 50 states)
- 64 deaths (more under investigation) (28 states)
Vaping Lung Injury Outbreak – California Data as of February 2020

E-cigarette or Vaping Associated Lung Injury (EVALI)
Update Report 2/11/2020

Table 1: Case Characteristics

<table>
<thead>
<tr>
<th>Total Cases</th>
<th>208</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of California counties reporting cases</td>
<td>31/58 (53%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>4 (2%)</td>
</tr>
</tbody>
</table>

Data below are updated as of 1/7/20 based on 192 cases

<table>
<thead>
<tr>
<th>Sex</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>119 (62%)</td>
</tr>
<tr>
<td>Female</td>
<td>73 (38%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>14-70 years</td>
</tr>
<tr>
<td>Median</td>
<td>25 years</td>
</tr>
</tbody>
</table>

Severity of Illness

<table>
<thead>
<tr>
<th>Required admission to Intensive Care Unit (total)</th>
<th>87 (45%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages 0-18</td>
<td>16</td>
</tr>
<tr>
<td>Ages 19-26</td>
<td>27</td>
</tr>
<tr>
<td>Ages 27+</td>
<td>44</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Required mechanical ventilation (total)</th>
<th>54 (28%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages 0-18</td>
<td>9</td>
</tr>
<tr>
<td>Ages 19-26</td>
<td>19</td>
</tr>
<tr>
<td>Ages 27+</td>
<td>26</td>
</tr>
</tbody>
</table>
Table 2: Case Interview Data

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Total Interviews Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>47 (42%)</td>
</tr>
<tr>
<td>Black</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>48 (43%)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Declined</td>
<td>5</td>
</tr>
</tbody>
</table>

Reported vaping practices in the past 3 months

<table>
<thead>
<tr>
<th>Vape Type</th>
<th>Total Interviews Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaped product containing THC</td>
<td>92 (83%)</td>
</tr>
<tr>
<td>Vaped product containing CBD</td>
<td>39 (35%)</td>
</tr>
<tr>
<td>Vaped product containing nicotine</td>
<td>51 (46%)</td>
</tr>
<tr>
<td>Vaped nicotine products only</td>
<td>10 (9%)</td>
</tr>
</tbody>
</table>
Timecourse of Cases in California

EVALI Hospital Admissions and Number of Reports by Week of Outbreak
(6/18/2019 - 2/10/2020)
What we know so far...

**PRODUCTS**
- THC oils (83% of cases)
- Nicotine only (9-10%) – accuracy of self-reporting?
- Vitamin E Acetate (70% of the THC oil users with 1 or more)

**SOURCES**
- Unlicensed ("informal") sources (majority, difficult to define) – 75% of cases

**DEMOGRAPHICS**
- Wide age range (14-70 yo), median = 25 yo
- 73% vaped daily. 35% more than 5 times/day

**CLINICAL**
- Unresponsive to antibiotics
- Responsive to corticosteroids
- Delay in onset of symptoms by days (median from last vaping = 3 days)
- Ground glass histology, “tree-in-bloom” opacities on scans
## Looking at Potential Causative Agents for EVALI

<table>
<thead>
<tr>
<th></th>
<th>Historical Exposure?</th>
<th>Consistent with EVALI?</th>
</tr>
</thead>
<tbody>
<tr>
<td>THC</td>
<td>Yes, cannabis smoking</td>
<td>No</td>
</tr>
<tr>
<td>Synthetic Cannabinoids</td>
<td>Yes, cannabis dabbing</td>
<td>No</td>
</tr>
<tr>
<td>Terpenoids</td>
<td>Yes, cannabis smoking/dabbing</td>
<td>No</td>
</tr>
<tr>
<td>Flavorings</td>
<td>Yes, nicotine vaping</td>
<td>No</td>
</tr>
<tr>
<td>Pesticides</td>
<td>Yes, cannabis smoking, occup. exp.</td>
<td>No</td>
</tr>
<tr>
<td>Metals</td>
<td>Yes, nicotine vaping</td>
<td>No</td>
</tr>
<tr>
<td>Coconut oil or other MCTs</td>
<td>Yes, THC vaping/dabbing</td>
<td>No</td>
</tr>
<tr>
<td>Microbial infection/Endotoxins</td>
<td>Yes, various</td>
<td>No ?</td>
</tr>
<tr>
<td>VEA and/or VE</td>
<td>No</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
Vitamin E Acetate – many questions

September 2019

New York State - many of the products had high % (16-57%) alpha tocopherol acetate (VEA)

• Found in many of the products and all (29/29) BAL cases initially. >90%.

• No known pulmonary toxicity (high doses?) (Hybertson et al., 2015). Low oral doses protective.

• VEA is synthetic. Poorly absorbed compared with vitamin E

• Overload phenomenon of lung clearance?
  • Why the delayed time course of symptoms/signs?
  • Why wouldn’t every person get the disease?
  • Did each and every case investigated have evidence of VEA exposure?

• Thermolysis products of vitamin E acetate?
Vitamin E as a Pulmonary Antioxidant

Vitamin E as an Antioxidant of the Lung
Mechanisms of Vitamin E Delivery to Alveolar Type II Cells

Ingrid Kolleck, Pranav Sinha, and Bernd Rüstow

Department of Neonatology and Institute of Pathobiochemistry and Laboratory Medicine, Charité Hospital, Humboldt University Berlin, Berlin, Germany

Oxidants play an important role in the development of acute and chronic lung injuries. Alveolar surfactant is the first target of airborne oxidants. Surfactant contains, besides dipalmitoyl phosphatidylcholine, cholesterol and polyunsaturated phospholipids that play an important functional role. Therefore, vitamin E could be important for protecting surfactant lipids against oxidation and subsequent lung injury. Alveolar type II cells play a central role in synthesis and secretion of surfactant lipids and also supplement the surfactant with vitamin E during intracellular assembly. High-density lipoprotein (HDL) is the primary source of vitamin E for type II cells. The uptake of vitamin E by specific lipid transfer is mediated by at least three HDL-specific receptors (scavenger receptor BI, membrane dipeptidase, and HDL-binding protein-2). In addition, cubulin and megalin mediate in a cooperative manner HDL-holoparticle uptake by alveolar type II cells. A temporary vitamin E deficiency induces a reversible change of the expression of pro- and anti-inflammatory markers and of markers defining apoptosis, and reduces surfactant lipid synthesis in alveolar type II cells. These metabolic changes of type II cells may prime the lung to develop clinically manifest injury in response to an additional insult, e.g., hyperoxia.

Keywords: lung; vitamin E; alveolar type II cells; high-density lipoprotein; scavenger receptor BI

Reactive oxygen species are thought to play an important role in the pathogenesis of lung injuries such as bronchopulmonary dysplasia and chronic obstructive pulmonary disease in newborn infants and in adults (1, 2). The damages caused by oxidant-induced changes in plasma and cells. The accumulation of oxidized lipids and proteins in alveolar epithelial cells is thought to be a major source of injury in the lung.
Patented Process for Vitamin E to Produce Cannabis Oil - 2016

(72) Inventors: FINLEY, Constance; c/o Constance Therapeutics, Inc., 500 Tremont Avenue, Point Richmond, California 94801 (US); MCKEE, Libbie; c/o Constance Therapeutics, Inc., 500 Tremont, Point Richmond, California

(54) Title: METHODS FOR PREPARATION OF CANNABIS OIL EXTRACTS AND COMPOSITIONS

(57) Abstract: The present invention provides cannabis oil extracts and compositions thereof, including cannabis oil compositions containing vitamin E, and methods for preparing the extracts and compositions. In some embodiments, the present invention provides a method for preparing a cannabis oil extract comprising extracting cannabinoids from cannabis plant material with a solvent to produce an eluate, filtering the eluate with a filter to produce a filtrate, evaporating the solvent from the filtrate with a distiller to produce a distillate, and purging the distillate under conditions sufficient to remove residual solvent, thereby preparing the extract. In some embodiments, the method further includes mixing a quantity of vitamin E with the extract to produce a cannabis oil composition.

[0043] The term "vitamin E" refers to a group of compounds that include both tocopherols and tocotrienols including, but not limited to, α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, salts thereof, and...
Why the Mechanism Matters

POLICY development:
If policy is specific to VEA but mechanism for EVALI is not directly related to VEA, then regulatory actions might result in regrettable substitutions

CLINICAL:
A better understanding of the mechanism may facilitate an improved therapeutic approach and outcome
The Evidence on Lipoid Pneumonia (Butt et al., 2019 NEJM)

**Conclusion:** EVALI patients do not have exogenous lipoid material in their lung macrophages.
'Chemical Burns' Seen as Possible Cause of Vaping Lung Damage

Lung injuries from vaping **probably result from direct toxicity or tissue damage caused by noxious chemical fumes**, rather than from an accumulation of lipids in the lungs, pathology data suggest.

"We were not surprised by what we found, regarding toxicity," Brandon T. Larsen, MD, PhD, a surgical pathologist at the Mayo Clinic, Scottsdale, Arizona, and a national expert in lung pathology, said in a news release. "We have seen a handful of cases, scattered individual cases, over the past two years where we’ve observed the same thing, and now we are seeing a sudden spike in cases. Our study offers the first detailed review of the abnormalities that may be seen in lung biopsies to help clinicians and pathologists make a diagnosis in an appropriate clinical context," Larsen said.

To learn more about the pathology of vaping-associated lung injury, Larsen and colleagues studied lung biopsy specimens from 17 patients (13 men; median age, 35 years) who reported vaping and who were suspected of having associated lung injuries. Two of the patients were from the Mayo Clinic, and the other patients were from elsewhere in the United States. Most (71%) of the patients vaped with marijuana or cannabis oils.

Larsen and colleagues’ findings were published online October 2 in the New England Journal of Medicine. All of the patients had bilateral pulmonary opacities; 15 of the patients presented in 2019.

All of the lung biopsy specimens revealed “patterns of acute lung injury, including acute fibrinous pneumonitis, diffuse alveolar damage, or organizing pneumonia, usually bronchiolocentric and accompanied by bronchiolitis,” the authors explain. Histologic findings were nonspecific, but all cases were characterized by foamy macrophages and pneumocyte vacuolization. Pigmented macrophages were sometimes seen, but these never predominated. There were often prominent neutrophils; eosinophils were seen rarely; and no granulomas were seen. Bronchoalveolar lavage fluid was available for two cases. They revealed “abundant foamy macrophages.” Two patients who had diffuse alveolar damage died.

The researchers saw no histologic or radiologic evidence of tissue damage resulting from an accumulation of lipids such as mineral oils, which until now have been a suspected cause of vaping-linked lung injuries.

"While we can’t discount the potential role of lipids, we have not seen anything to suggest this is a problem caused by lipid accumulation in the lungs. Instead, it seems to be some kind of direct chemical injury, similar to what one might see with exposures to toxic chemical fumes, poisonous gases and toxic agents," Larsen

*New Engl J Med.* Published online October 2, 2019.
Fitting the Pattern of Toxicity

- ‘New’ in public health
- Highly toxic but without good warning properties
- Formed under heat and in presence of heating element
- Extremely toxic to the lung, with a delayed onset of symptoms
- Forms in mostly hydrophobic conditions
# Physical/Chemical Properties of Vaping Products

## THC vs Nicotine and Carrier Physical Properties

<table>
<thead>
<tr>
<th>Property</th>
<th>THC</th>
<th>Vitamin E acetate</th>
<th>Nicotine</th>
<th>Propylene glycol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boiling point (°C)</td>
<td>155-160</td>
<td>184</td>
<td>247</td>
<td>188</td>
</tr>
<tr>
<td>Water solubility (mg/L)</td>
<td>2.8</td>
<td>&lt; 1</td>
<td>1,000,000</td>
<td>1,000,000</td>
</tr>
</tbody>
</table>

“Propylene glycol and glycerol are both hygroscopic, thus e-liquid will always contain at least a small amount of water, whether by design or happenstance.”

- Jensen, 2016
Acute respiratory distress syndrome due to exposure to high-concentration mixture of etheneone and crotonaldehyde

Jun-Feng Huang¹, Du-Ming Zhu¹, Jie-Fei Ma¹ and Ming Zhong¹

Abstract
Introduction: Acute inhalational exposure leads to rapidly progressive acute respiratory distress syndrome (ARDS). This report is the first one to present a patient with ARDS in relation to long-standing exposure to a high-concentration mixture of etheneone and crotonaldehyde. Case report: A male worker in a chemical plant was accidentally exposed to the mixture of high-concentrated etheneone and crotonaldehyde for 5 min in an open space and worked continuously in the polluted area for approximately 12 h. On admission, he was conscious with the following vital parameters: blood pressure, 151/91 mmHg; pulse rate, 107 beats/min; respiratory rate, 30 breaths/min; temperature, 37.6°C; oxygen saturation, 92% preserved by mask saturation 10 L/min; arterial blood gases showed P/F oxygen ratio of less than 200. Physical examination disclosed decreased bilateral vesicular sounds. A chest computed tomography revealed bilateral nongaseous and ground-glass opacities. The patient was mechanically ventilated and treated with corticosteroids. The patient was discharged without any symptoms. Conclusion: Exposure to mixtures of etheneone and crotonaldehyde can cause severe pulmonary injury leading to delayed ARDS.

Keywords
Acute lung injury, acute inhalation injury, corticosteroid, ARDS, acute inhalational exposure

Ethenone – aka “ketene”

*Delayed ARDS after 5 min
*Ground glass opacity
*Corticosteroids
What is Ketene?

...and why have we never heard of it...?
How is Ketene Formed?

“In the laboratory, ketene is prepared easily in a “ketene lamp”, in which acetone vapors are passed over an electrically-heated tungsten wire at about 700°C (Cameron and Neuberger 1937; Hasek 1981).”

Toxicity of Ketene

“Ketene, like phosgene, acetylates free amino groups of proteins…”

“…phosgene and ketene may affect enzymatic activity in lung cells in a similar way, suggesting that their modes of action could be similar.”

“Similar to phosgene, the delay in toxicity observed with ketene results from the acylation of essential functional groups of enzymes and proteins in the lung rather than direct irritation by ketene or metabolites (Sciuto 2005).”

# Ketene Descriptive Toxicity in Experimental Animals
(10-min exposures)

<table>
<thead>
<tr>
<th>Species</th>
<th>Ketene concentration (ppm)</th>
<th>Mortality</th>
<th>Time to death (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>250</td>
<td>0/2</td>
<td>3 - 10</td>
</tr>
<tr>
<td></td>
<td>375</td>
<td>2/2</td>
<td></td>
</tr>
<tr>
<td>Mouse</td>
<td>25</td>
<td>0/10</td>
<td>1 - 16</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>8/20</td>
<td></td>
</tr>
<tr>
<td>Guinea pig</td>
<td>375</td>
<td>0/2</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>1/2</td>
<td></td>
</tr>
<tr>
<td>Rabbit</td>
<td>750</td>
<td>0/2</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>1000</td>
<td>1/2</td>
<td></td>
</tr>
<tr>
<td>Monkey</td>
<td>50</td>
<td>0/1</td>
<td>7.7</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>1/1</td>
<td></td>
</tr>
<tr>
<td>Cat</td>
<td>200</td>
<td>0/1</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>750</td>
<td>1/1</td>
<td></td>
</tr>
</tbody>
</table>

Ketene highly acutely toxic to multiple species, mice and primates most sensitive

Lung the target organ. No evidence for acute systemic effects

Treon et al., 1949 (cited in NRC 2014)
# Ketene Acute Emergency Guideline Levels (AEGLs)

<table>
<thead>
<tr>
<th>CLASSIFICATION</th>
<th>10-min</th>
<th>30-min</th>
<th>1-hour</th>
<th>4-hour</th>
<th>8-hour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AEGL-1 (NON-DISABLING)</strong></td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>AEGL-2 (DISABLING)</strong></td>
<td>0.08</td>
<td>0.08</td>
<td>0.063</td>
<td>0.04</td>
<td>0.029</td>
</tr>
<tr>
<td><strong>AEGL-3 (LETHAL)</strong></td>
<td>0.24</td>
<td>0.24</td>
<td>0.19</td>
<td>0.12</td>
<td>0.088</td>
</tr>
</tbody>
</table>

Concentrations in ppm

**EXPOSURE DURATION**


**Conclusion**: Ketene is super toxic to the lung (Category 1, under GHS Classification)
Potential for Release of Pulmonary Toxic Ketene from Vaping Pyrolysis of Vitamin E Acetate

Dan Wu* and Donal F. O’Shea*

Department of Chemistry, RCSI, 123 St. Stephen’s Green, Dublin 2, Ireland.

email: donalfoshea@rcsi.ie and danwu@rcsi.ie

A combined analytical, theoretical and experimental study has shown that the vaping of vitamin E acetate has the potential to produce exceptionally toxic ketene gas, which may be a contributing factor to the upsurge in pulmonary injuries associated with using e-cigarette/vaping products. Additionally, the pyrolysis of vitamin E acetate also produces carcinogen alkenes and benzene for which the negative long-term medical effects are well recognized. As temperatures reached in vaping devices can be equivalent to a laboratory pyrolysis apparatus, the potential for unexpected chemistries to take place on individual components within a vape mixture is high. Educational programs to inform of the danger are now required, as public perception has grown that vaping is not harmful.

Keywords

Vitamin E acetate; ketene; vaping; pyrolysis; lung injury
Thermolysis Products of Vitamin E Acetate

Source: Wu and O'Shea, 2019
Acetone and Acetates

Acetone is a well known solvent for THC extraction

Wide variation in acetone content, non-detect to >150 ppm*

....Acetone, VEA, what about other acetates as starting materials?

*unpublished CDPH data
Ketene Formation from Carboxylic Acids

United States Patent


[54] CATALYST AND PROCESS FOR SYNTHESIS OF KETENES FROM CARBOXYLIC ACIDS

[75] Inventors: P. C. Watson, Elkton, Md.; M. C. Libby, West Henrietta, N.Y.; M. A. Barteau, Wilmington, Del.

[73] Assignee: The University of Delaware, Newark, Del.

[21] Appl. No.: 255,348

[22] Filed: Jun. 8, 1994

[51] Int. Cl. 5 .............................. C07C 45/89

[52] U.S. Cl. .............................. 568/301; 568/302

[58] Field of Search .......................... 568/301, 302

[56] References Cited

U.S. PATENT DOCUMENTS

5,438,650 12/1995 A. A. K. 5,400,139


“The acidity of silica surfaces”, Hair, M. L. in “Silicon Chemistry” (E. R. Corev, J. Y. Corev and P. O. Gaspar, Eds.).

Including fatty acids, propionic, butyric, valeric acids
Ketene Formation Using Catalysts, Using Silica

Watson et al., 1994 patent:

“The above results clearly demonstrate the efficacy of high surface area silicas for the production of ketenes from carboxylic acids. They further demonstrate that the surface area need not be limited to achieve selectivity, and that ketene yield increases with both silica surface area and hydroxyl population. Comparison of the dehydration behavior of C$_2$ - C$_5$ carboxylic acids in both TPD and steady state catalysis experiments demonstrates that the selectivity of ketene production by this route does not exhibit a strong dependence on carbon number.”
Sources of Acetates in Vaping Liquids

- VEA – under heat (Wu and O’Shea, 2020)
- Some flavorings (e.g. ethyl acetate, benzyl acetate)
- Butane, other solvents?
- Triglycerides/oils as a source of acetate?
- Glycols?
Formation of Acetates from Butane using Cobalt

Reaction temp: 75-130 C
Metal Filament Composition

Literature on metals in e-liquids:

Nickel
Chromium
Lead
Manganese
Cobalt
Copper
Zinc
Ceramic (silica based?) heating components
Ceramics as Catalysts

Ceramics for catalysis

M. A. KEANE
Department of Chemical and Materials Engineering, University of Kentucky, Lexington, KY 40506-0046, USA
E-mail: mkeane@engr.uky.edu

The use of ceramics as heterogeneous catalysts represents an extension of “non-traditional” ceramics applications and is now a burgeoning topic of research. In this Review, the principles of heterogeneous catalysis are presented and discussed in terms of surface reactivity and catalyst structure in general. Catalytic selectivity, rate enhancement and catalyst deactivation are addressed. The critical (bulk and surface) structural features that impact on catalyst performance are identified along with a survey of catalyst characterization techniques. Ceramics applications in catalysis are divided into (i) direct use as catalysts and (ii) use as support materials (substrates) to anchor and disperse a variety of active metals. Practical ceramic catalysts are typically complex metal oxides containing at least two different cations which offer enormous compositional flexibility, as is discussed in the case of perovskite oxides. Taking a broad definition of ceramics as “any inorganic nonmetallic material,” there is a wide array of catalysts that can be termed ceramics with disparate end uses. For the purposes of illustration, three established systems are discussed that each illustrates the role of ceramic materials in practical heterogeneous catalysis: (i) catalysis using zeolites; (ii) catalytic converters; (iii) solid oxide fuel cells.

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How Does CCELL Achieve It?

The unique patented ceramic formula is one of the key answers. Special manufacturing process of high temperature sintering enables it to process myriad nanoscale interior holes. Hence CCELL excels at absorbing, storing and vaporizing high viscosity extracted oil without any problem. Moreover, embedded coil was designed with reasonable resistance and equivalent gaps. All the above features combined with high performance battery makes CCELL capable of providing high vaporizing efficiency, even heat distribution, steady and consistent vapor, large vapor volume, pure flavor and powerful potency.
Formation of Ketene in oil Vaping: The Perfect Storm?

Ni, Cr, Co, Cu, Pb, Zn, Zr metal or ceramic/silica in filament, battery leads, and housing

mouthpiece

Battery cartomizer

Vitamin E Acetate, oil + THC/CBD +/- Acetone, etc

200-400°C

H₂O
Revisiting Hypotheses

THC/CBD (and acetate?)
Coconut oil (MCTs)?
**Vitamin E acetate**
Flavorings? Acetates?
Pesticides?
Terpenoids?
Synthetic cannabinoids?
Solvents/VOCs?

Can these form ketene under heat with metal/ceramics?

...and what about H₂O content?
Summary

* EVALI cases began in early-mid 2019
* Delayed onset of acute/subacute severe pulmonary damage
* No reports of significant membrane irritation

* VEA in many patients/products, but not known to be toxic to the lung
* Why vaping VEA acutely toxic to some people but not others?
* Overload VEA/lipoid pneumonia discounted by some pathologists.

* Ketene fits the toxicology/pathology
* Ketene is formed from VEA
* Acetates and acetone are precursors in presence of metals and heat, under anhydrous conditions
* These conditions exist in some THC vaping devices
* Ketene is elusive and difficult to directly detect – research underway...
* Only small ppm concentrations of ketene needed to cause acute lung damage (similar to phosgene gas). Chronic low doses have not been studied.
Conclusions

Hydrophobic oils like VEA should be considered unsafe for vaping. Role of water content?

It is unclear if water soluble oils, like coconut oil, also carry a degree of risk. Carboxylic acids generally?

Residual solvents, like acetone, butane, ethanol, ethyl acetate, etc..., could play a role in ketene formation and should to be strictly regulated in all vaping products.

The role of specific metals or ceramics in catalyzing acetate and ketene formation needs to be studied.
Pre-print: Attfield et al., 2020. Potential of Ethenone (ketene) to Contribute to E-cigarette, or Vaping, Product Use–Associated Lung Injury
References


Huang J, Zhu D, Ma J, Zhong M. Acute respiratory distress syndrome due to exposure to high concentration mixture of ethenone and crotonaldehyde. Toxicol Ind Health 2015; 31(7):585-587.


Wu D, O'Shea D. Potential for formation of pulmonary toxic ketene from vaping pyrolysis of vitamin E acetate. 2020 PNAS (in press).
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Donal O’Shea, MD, PhD (RCSI)
Gordon Vrdoljak, PhD (CDPH)
Ping Wang, PhD (CDPH)
Jeff Wagner, PhD (CDPH)
Jason Wilkens, PhD (US CDC)
Dadong Xu, PhD (CDPH)